H_1 antihistamines: psychomotor performance and driving

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As has already been extensively commented in the article on antihistamines and the central nervous system, published in this same issue, all the classical antihistamines and, to a lesser extent, the more recent synthetic compounds are able to exert depressive action upon the central nervous system (CNS), causing drowsiness, lassitude, dizziness, incoordination, and increased reaction time. Moreover, in many cases they also induce peripheral neurological effects secondary to cholinergic block (dilatation of the pupils, blurry vision, or dry mouth), which can affect patient ability to drive.

According to information from the traffic authorities, in Spain each year motor vehicle accidents cause 5000 deaths and 130,000 injuries – the majority affecting people under 40 years of age. At least one-third of these accidents are due to human factors related with the driver, including alcohol consumption, risk behavior and, in some cases, drug substances [1]. In 2004 the *Comisión Profesional de Sociedades Sanitarias para la Prevención de Lesiones por Accidentes de Tráfico* (COSPLAT) was created, comprising 38 medical societies, including the *Sociedad Española de Alergología e Inmunología Clínica* (SEAIC). The joint objectives of the SEAIC and COSPLAT include the elaboration of a list of antiallergic medicines, the use of which should be limited among drivers, and the recommendations of the medical community regarding the prescription of other, safer alternatives [2].

Patients treated with antihistamines are largely outpatients, and so therefore also habitual drivers. As has also been extensively documented in other articles of this same issue, all the first generation antihistamines, and many of the second generation drugs (ketotifen, loratadine, ebastine, mizolastine, rupatadine), undergo total or partial liver metabolization through isoenzymes of the cytochrome P450 system (CYP3A4, CYP2D6). In addition, to one degree or other, they interact with alcohol (reinforcement of sedative effects) and with other drugs that make use of the same metabolic pathways (macrolides, imidazoles, H2 antihistamines, serotonin reuptake inhibitors), thus giving rise to unpredictable increases in the plasma levels of the antihistamine, and to prolonged elimination rates [3]. All this must be taken into account when antihistamines are used by habitual drivers, and particularly by professional drivers.

Physiology of the central effects of antihistamines

As has already been extensively commented in the article on antihistamines and the central nervous system, published in this same issue, the histaminergic neurons in the CNS are mainly located in the hypothalamus (tuberomammillary nucleus), though with connections to the entire brain, and exhibit a great many markers of other neurotransmission systems [4]. Histamine as a neurotransmitter influences alertness or cortical activation and the sleep-waking cycles, fundamentally through activation of its H_1 receptors.

To one degree or other, the CNS contains all four known transmembrane histamine receptors (H_1, H_2, H_3 and H_4), belonging to the family of membrane G protein bound receptors. As with most of these, they are in a state of balance between their active and inactive conformations [5]. The H_1 antihistamines act as inverse agonists, i.e., activating the inactive conformations of the H_1 receptors [6], the distribution of which is very extensive in brain areas related to the waking state and cognition. Thus, the sedative effects are directly proportional to their capacity to cross the blood-brain barrier (BBB), which in turn depends on the degree of lipophilicity and on the size of the molecule, and to a lesser extent on its binding to serum proteins and apparent distribution volume [7]. On the other hand, many H_1 antihistamines can induce direct neurological effects through cholinergic and serotoninergic block. Moreover, the occupation of these H_1 receptors could

allow circulating histamine to saturate other receptors, such as the central H_3 receptors, which can also induce sedation [8].

Saturation of the central H_1 receptors can be measured directly by radioimaging techniques such as positron emission tomography (PET) with labeled ^{11}C-doxepin, which shows a greater potential for binding to the receptors the lesser they are already blocked by another circulating antihistamine [9]. Thus, it can be shown that the classical antihistamines, possessing a lipophilic structure, occupy about 75% of the H1 receptors in the brain, while in comparison the new and more polar compounds (of a hydrophilic nature) only occupy up to 25% of these same central receptors.

Cognitive and neurophysiological tests in the study of antihistamines

In the study of the effect of antihistamines and of other drugs upon psychomotor performance, use has been made of a series of subjective and objective tests and examinations (summarized in Table 1).

1. Subjective psychomotor tests

- ***Data from clinical trials.*** Adverse events spontaneously reported by patients in clinical trials with large series of subjects with rhinitis or urticaria.
- ***Scales of drowsiness.*** A number of standardized

Table 1. Tests evaluating the effect of antihistamines upon psychomotor performance.

1. SUBJECTIVE TESTS. Questionnaires with specific items addressing drowsiness or lassitude: Stanford drowsiness scale, visual analog scales, and others.

2. OBJECTIVE PSYCHOMOTOR TESTS

Sensory-motor coordination tests
- Critical tracking test
- Oculomotor coordination
- Total reaction time: Simple + complex

Evaluation of cortical functions
- Processing: Mental calculation tests
- Integration: Critical flicker fusion
- Memory: Digit span or numerical tests
- Learning: Word list

Evaluation of sensory functions and alertness
- Detection of stimuli: Hearing alertness, dynamic visual acuity
- Perception: Cancellation, spatial perception, color test
- Recognition: Digit symbol substitution

Evaluation of motor functions
- Coordination: Manual skill
- Others: Tapping, body sway, hand tremor

3. NEUROPHYSIOLOGICAL TESTS

EEG recordings:
- Continuous EEG monitorization
- Multiple sleep latency test

Auditory evoked potentials: P-300

4. SIMULATED DRIVING AND PILOTING TESTS

5. REAL DRIVING TESTS

Protocolized driving in healthy volunteers (Highway Driving Test)
Secondary driving test (Car-Following Test)

Table 2. Stanford drowsiness scale.

1. I feel active, vital, alert, well awake.
2. I am at a high level, but not at top performance. I am able to concentrate.
3. Relaxed, awake but not completely alert, responsive.
4. Somewhat drowsy, slowed.
5. Drowsy, beginning to stop my activity, hard to stay awake.
6. Sleepy, I prefer to lie down.
7. Almost disconnected, cannot stay awake, about to fall asleep.

scales are available, such as the Stanford (Table 2), Leeds, or Epworth scales [10], as well as visual analog scales (VAS).

2. Objective psychomotor tests

Many objective laboratory tests are commonly used to evaluate the effect of drugs on different higher cortical functions, motor capacity, coordination and sensory capacity (detection, perception and recognition of external stimuli). In the study of antihistamines, the measurement of reaction time has been shown to be particularly sensitive, as well as critical flicker fusion. These are the most commonly used tests, together with simulated and real driving tests [11].

- **Reaction time** (Choice Reaction Time). This test globally evaluates psychomotor performance. The test subject places a finger on a panel and is required to turn off one of six equidistant and randomly illuminated lights, by pressing the correct button. Measurement is made of the time taken to recognize the stimulus (simple reaction time), and of motor response velocity (complex reaction time), in milliseconds, in the course of 50 consecutive attempts [12].
- **Critical flicker fusion.** This test measures alertness and integration functions. The subject defines the frequency required for a sequence of blinking lights to remain fixed or continuous [12].

3. Neurophysiological studies

The most common studies in the investigation of antihistamines are EEG (electroencephalogram) recordings, such as the multiple sleep latency test (the time needed to induce phase 1 EEG sleep after repeated opportunities for diurnal sleep under protocolized conditions), and studies with auditory evoked potentials, such as the P-300 test, which reflect the speed of the active cognitive processing of information and its modification by different drugs [13]. These studies generally show good correlation with the cognitive tests [10].

Over 80 comparative studies (randomized, double blind, placebo controlled, cross-over) using psychometric and/or neurophysiological tests have documented evident and significant differences in psychomotor performance between the first and second generation antihistamines. In this context, many studies have focused on cetirizine, loratadine, ebastine, fexofenadine, mizolastine, acrivastine, desloratadine, levocetirizine, and also topical antihistamines [3]. However, comparative studies between different second generation antihistamines are anecdotal and inconclusive [14].

Epidemiological studies on antihistamines and driving

National and international epidemiological studies on the possible role of antihistamines in relation to traffic accidents are relatively scarce, and their results are moreover difficult to interpret.

1. Descriptive cross-sectional studies [15]. These have been carried out among drivers. The most salient observation in studies of this kind is the fact that self-medication and the simultaneous consumption of alcohol is common practice. Seventeen percent of the drivers are found to consume medication on a habitual basis, and up to 5% regularly use drugs known to alter the ability to drive. In turn, 63% admit consuming alcohol at least once a week.

Table 3. Analytical studies on drugs and the risk of accident [15].

Study	Results	RR	p/95%CI
Skegg (1979)	Sedatives	5.2	p<0.01
	Minor tranquilizers	4.9	p<0.01
	Major tranquilizers	6.3	p<0.05
Ray (1992)	Psychoactive drugs	1.5	1.2-1.9
	Benzodiazepines	1.5	1.1-2.0
	Tricyclic ADs	2.2	1.3-3.5
Leville (1994)	Benzodiazepines	0.9	0.4-2.0
	Tricyclic ADs	2.3	1.1-4.8
	Opiate analgesics	1.8	1.0-3.4
	Antihistamines	0.7	0.3-1.7
Herings (1995)	Medications with warnings of potential effects on the ability to drive	1.9	p<0.01

RR = relative risk; CI = confidence interval; ADs = antidepressants

2. Analytical studies (case-control or retrospective cohort surveys). Studies of this kind have been used to try to demonstrate an increased risk of accident among people who use a drug versus those who do not. Such surveys have been conducted in the general population and in drivers over 65 years of age, involved or not in traffic accidents. Few such studies have included antihistamines, and the observed relative risk (RR) is generally low (Table 3) [15].

3. Determination of substances in the biological fluids of traffic accident victims (deaths or injuries), and analysis of risk according to the concentration of the drug or toxic agent. A prevalence of antihistamines of up to 0.6% has been documented, though adequate control groups are not available [16]. Thus, according to the existing epidemiological data, the relative risk of antihistamines in the occurrence of traffic accidents is low compared with other groups of drugs such as sedatives or hypnotics. However, the scant available data make it necessary to conduct specific experimental studies involving simulated and real driving conditions.

Experimental simulated driving and flight studies

Driving simulators are used as a complement to psychomotor testing. They aim to demonstrate the true effect of antihistamines in situations of driving and piloting. Flight simulators are mainly used, due to the impossibility of testing under real flight conditions [17].

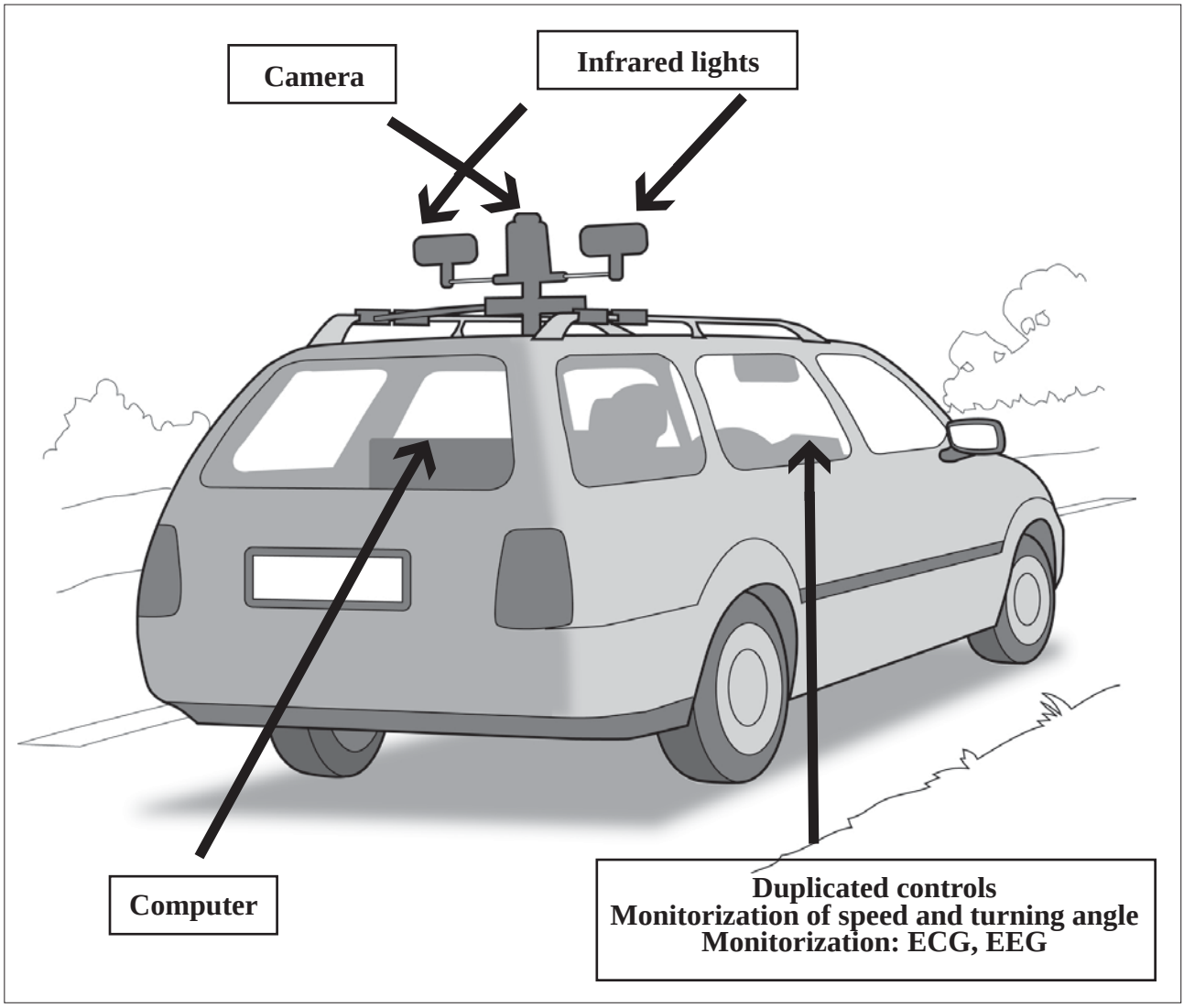

Figure 1. The current studies involving real driving conditions (Highway driving test) are carried out during normal traffic in adapted automobiles with duplicated controls, camera, infrared distance sensors, and a computer to monitor speed, angle of turn and deviation from midline.
ECG: electrocardiogram.
EEG: electroencephalogram.

Experimental real driving studies

In principle, studies of driving under real conditions were made in closed circuits, due to the potential hazards for other drivers, and the consequent problems for obtaining authorization to conduct such tests under real life conditions.

However, during the eighties, in Maastricht (The Netherlands), a protocolized driving test under normal traffic conditions was developed [18], and since then many studies have been made on a double blind basis versus placebo, in healthy volunteers. The tests are made using specially adapted vehicles with duplicated controls, a roof-installed camera, infrared distance sensors, and a computer (Figure 1). The vehicle is occupied by the test subject, a supervisor (driving school instructor), and a technician. The vehicle is able at all times to measure speed, angle of turn of the steering wheel, and lateral deviation with respect to the road lines. ECG (electrocardiogram), EEG and eye movement monitorization is also available. Based on these vehicles, deviation tests are conducted both on highways and on a car-following principle.

1. Protocolized driving in healthy volunteers (Highway Driving Test).

Table 4. Legal blood alcohol limits and lateral position standard deviation (LPSD) [19].

BLOOD ALCOHOL CONCENTRATION	LPSD
0.05%	+ 2.6 cm
0.08%	+ 4.1 cm
0.10%	+ 5.3 cm

Driving of the adapted vehicle on the highway, in a 100-km circuit (50 km either way) at a constant speed (90-95 km/h) and in stable position in the right lane, with recording of the entire trajectory. The principal parameter measured is the capacity to keep the vehicle in the center of the lane, which is expressed as the lateral position standard deviation in cm (LPSD) (Figure 2) [19]. This is calibrated with respect to previous determinations made under experimental conditions for different legal blood alcohol limits, and versus placebo (Table 4).

2. Car-following test. This experiment particularly evaluates driver capacity to adjust speed to that of the vehicle ahead, and to respond to its braking lights (Brake

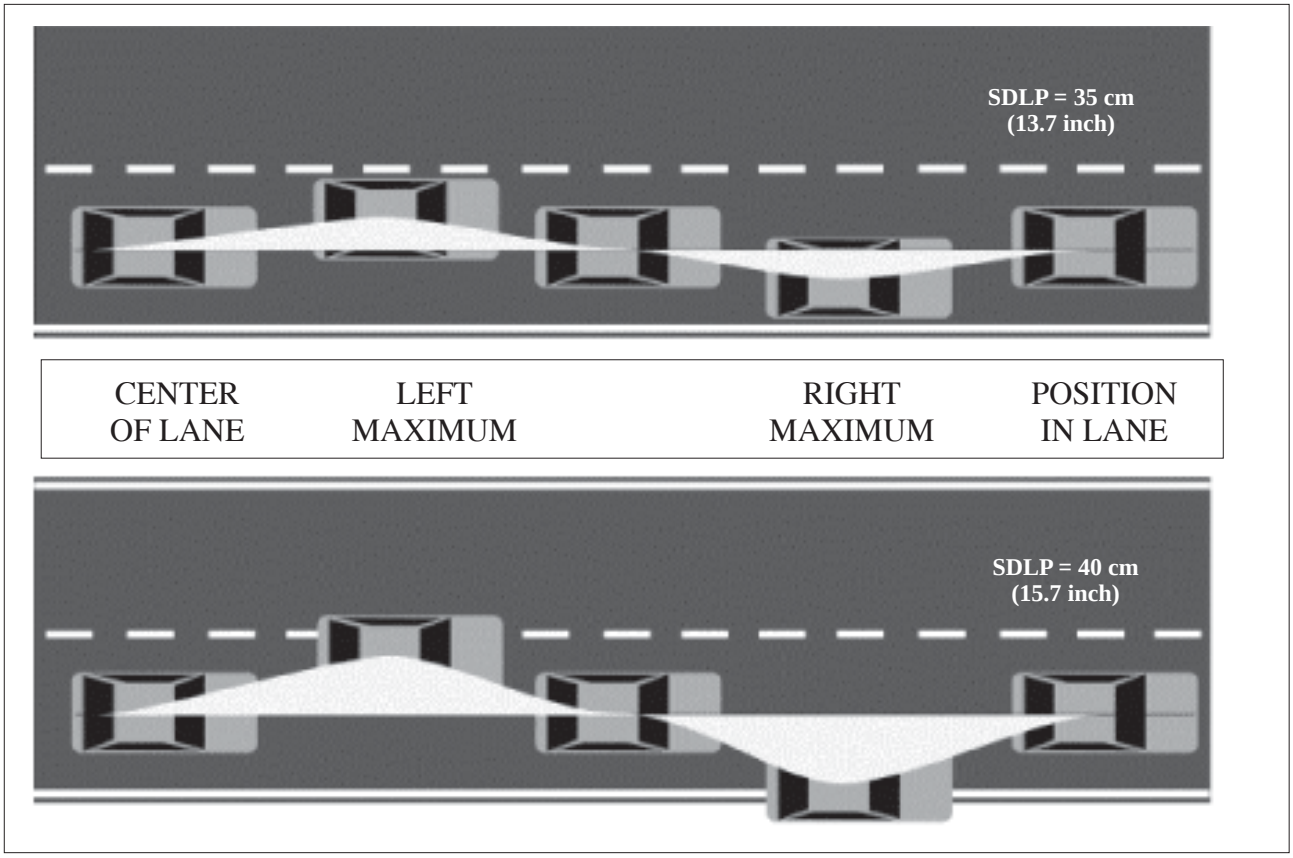

Figure 2. In the protocolized driving test in healthy volunteers (Highway Driving Test), the principal parameter measured is the capacity to keep the vehicle in the center of the lane, which is expressed as the lateral position standard deviation in cm (LPSD) [19].

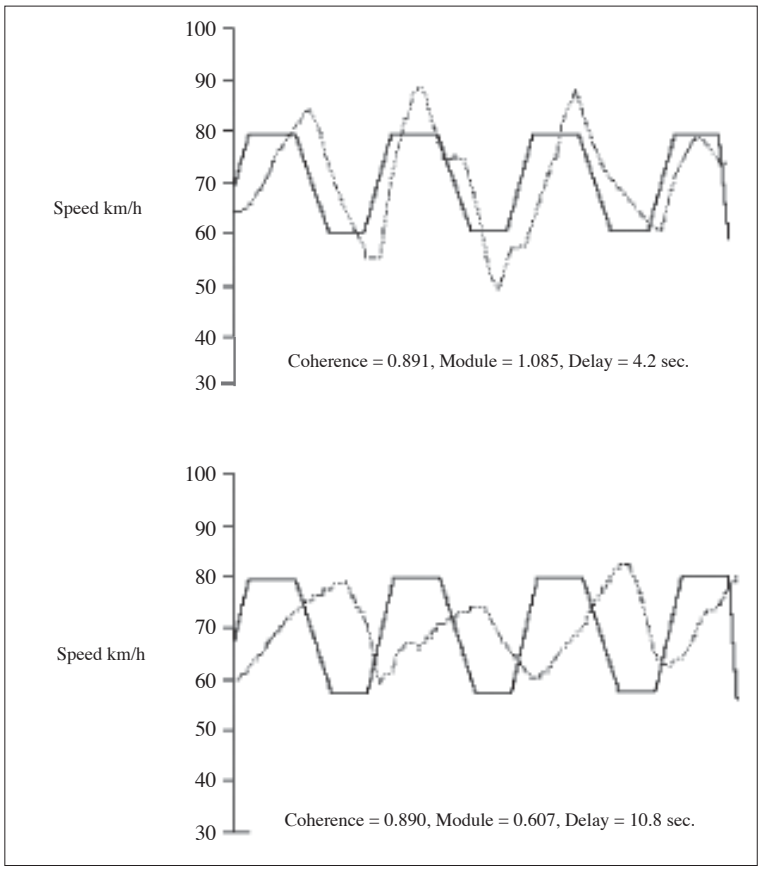

Figure 3. Car-following test. Speed signs in two automobiles driven by the same participant: Top: without prior medication. Bottom: after diphenhydramine 50 mg. Reproduced with permission from [20].

Table 5. First generation antihistamines under real driving conditions (Modified from Verster JC, ref. 19).

Drug	Dose	n	Sex	Day 1 (single dose)	Day 4 (dosis diaria)
Triprolidine	10 mg/day (DR*)	20	Males	SD	Not tested
	5 mg/12 h.	24	Mixed	SD	SD
	10 mg/day	15	Males	SD	NS
	5 mg/12 h.	27	Males	SD	SD
	10 mg/day (DR*)	15	Males	NS	NS (5th day)
Diphenhydramine	50 mg/ day?	18	Females	SD	Not tested
	50 mg/ day?	48	Mixed	SD	SD
Clemastine	2 mg	24	Mixed	SD	Not tested
	2 mg/12 h	25	Mixed	SD	SD
Dexchlorpheniramine	6 mg (DR) / day?	18	Mixed	SD	Not tested
	6 mg (DR) / day?	15	Mixed	SD	NS

*DR = delayed release. SD: significant difference versus placebo. NS: nonsignificant

Reaction Time). The test measures parameters such as coherence or exactness in adjusting to speed, the amplification factor or module between the two signals, and the delay or displacement of one signal with respect to the other (Figure 3) [20].

A recent review of 16 double blind studies versus placebo involving different antihistamines [19] and using these protocolized driving tests in health volunteers concluded the following (Tables 5 and 6):

• The first generation antihistamines significantly affect driving ability, both after single dosing and in the context of repeated daily dosing.

• The second generation antihistamines such as mequitazine, cetirizine, loratadine, ebastine, mizolastine, acrivastine or emedastine can also affect driving ability, though in a very variable manner depending on the dose

Table 6. Non-sedating antihistamines under real driving conditions (Modified from ref. 19).

Drug	Dose (mg)	n	Sex	Day 1 (single dose)	Day 4 (daily dose)
Mequitazine	5, 10, 15 mg	18	Mixed	NS	Not tested
	10 mg	15	Mixed	p<0.05	NS (8th day)
Terfenadine	60 mg/12 h.	27	Males	NS	NS
	120 mg/day	27	Males	NS	NS
	60, 120, 180	18	Females	NS	NS
Ebastine	10, 20, 30 mg	15	Males	NS	NS (5th day)
Loratadine	10, 20 mg	20	Males	NS	Not tested
	10 mg	16	Mixed	NS	NS
	20 mg	24	Mixed	NS	NS
Mizolastine	5 mg	24	Mixed	NS	NS
	10, 20, 40 mg	24	Mixed	p<0.05	NS
Cetirizine	10 mg	27	Males	NS	NS
	10 mg	16	Mixed	p<0.05	NS
	10 mg	19	Mixed	NS	NS
	10 mg	18	Mixed	NS	Not tested
Fexofenadine	120, 240	25	Mixed	NS	NS
Rupatadine	10 mg/24 h	22	Mixed	NS	NS
Levocetirizine	5 mg	48	Mixed	NS	NS

SD: significant difference versus placebo. NS: non significant

and interval between dosing and testing, and tolerance moreover generally develops within 4-5 days. The greatest differences versus placebo corresponded to emedastine [21]. For the second generation antihistamines such as fexofenadine or levocetirizine, the results versus placebo and alcohol likewise have been optimum in studies involving healthy volunteers. Comparative studies (in the real driving context) among second generation antihistamines are scarce and inconclusive.

• The association of antihistamines with alcohol shows additive effects in relation to impairment in the ability to drive – this having been confirmed at least for some antihistamines such as cetirizine and loratadine [22].

• In general, the combination of second generation antihistamines with pseudoephedrine revealed no true improvement in psychomotor performance and the ability to drive versus the antihistamine alone [23]. In any case, such an improvement would only appear after several days of administration, since the concentrations of pseudoephedrine accumulate over time [24].

• At present, no real driving studies have examined the effects of antihistamines involving the concomitant use of other medicines.

Limitations of the studies under real driving conditions

Individual variability. The studies are made in healthy volunteers, not in patients with disorders (allergic rhinitis) that intrinsically may cause drowsiness. On the other hand, in most of the studies interindividual variability is evident in terms of how drugs affect performance.

Variability of blood concentration. The effect of the antihistamines on driving ability is dose-dependent, but there is no lineal relationship between blood concentration and the degree to which psychomotor performance is affected – though the studies are usually made with maximum plasma levels (1-4 hours after dosing) [19].

Variability according to gender [19]. Women have been shown to be more sensitive to the sedative effects of some antihistamines (acrivastine, emedastine, cetirizine), while in studies with clemastine, mizolastine, fexofenadine and levocetirizine [25] no differences between males and females have been recorded.

Conclusions

Antihistamines are very often used by habitual drivers, and in many cases they may induce CNS depression as well as peripheral neurological effects secondary to anticholinergic action, that may affect the ability to drive. Although the epidemiological studies made to date have shown no important relative risk associated with antihistamines in terms of traffic accidents, the cognitive tests and experimental studies made under conditions of real driving suggest that first generation antihistamines should be avoided by drivers. The second generation antihistamines can also affect the ability to drive, though in a very variable manner, and in general tolerance develops within 4-5 days. Comparative studies under true driving conditions among second generation antihistamines are scarce and inconclusive.

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